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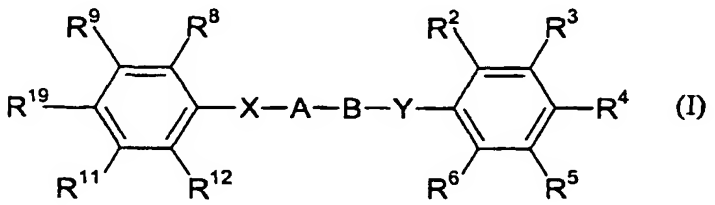
(54) Title: SALICYLATE ANALOGS AS INTERLEUKIN-4 ANTAGONISTS



(I)

(57) Abstract: Salicycate analogs of formula, methods of making them, pharmaceutical compositions containing them, and methods for their use. The compounds are interleukin-4 antagonists, and are useful for the treatment of asthma and allergies.

SALICYLATE ANALOGS AS INTERLEUKIN-4 ANTAGONISTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention relates to antagonists of interleukin-4 signaling. In particular, this invention relates to certain salicylate analogs that antagonize interleukin-4 signaling, to methods of making them, to pharmaceutical compositions containing them, and to their uses.

DESCRIPTION OF RELATED ART

Interleukin-4 (IL-4) is a pleiotropic cytokine that is produced primarily by T helper type 2 lymphocytes (TH2 cells). The most clinically significant activity of this cytokine is the stimulation of immunoglobin class switching of the immune system's B-cells to IgE production. See P. Chomarat et al., "An update on interleukin-4 and its receptor", *Eur. Cytokine Netw.*, **8**(4), 333-344 (1997); R. A. Pauwels et al., "Cytokines and their receptors as therapeutic targets in asthma", *Clin. Exp. Allergy*, **28**(Suppl. 3), 1-5 (1998), and references discussed therein.

Ample evidence exists that antagonism of IL-4 can alleviate allergic responses. These include the correlation of allergy and asthma symptoms with IL-4 levels in both allergen immunotherapy and asthma patients, the reduction of spontaneous IgE production in lymphocytes following treatment with IL-4 antibodies, and the inability to induce asthma-associated eosinophilia in IL-4 gene knockout mice. Additional evidence exists correlating elevated levels of IL-4 with osteoporosis, osteoarthritis, rheumatoid arthritis, and autoimmune and other inflammation related disorders. Antagonism of IL-4 might further prove useful for therapeutically desirable immunosuppression.

The attractiveness of developing a drug that antagonizes IL-4 activity has not escaped the pharmaceutical industry. Immunex and Wyeth-Ayerst are developing a nebulized form of a soluble IL-4 receptor for the treatment of moderate asthma. The drug, Nuvance, is now in

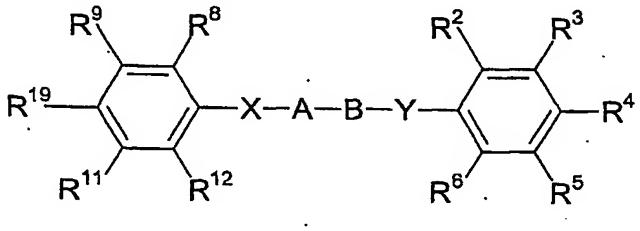
Phase II clinical trials. Glaxo SmithKline is developing an IL-4 antibody that is currently in clinical trials for the treatment of asthma.

Small molecule IL-1 antagonists have been sought. See R. Sarabu, "Design and synthesis of small molecule interleukin-1 receptor antagonists based on a benzene template, *Drug Design Discovery*, **15**, 191-198 (1998).

It would be desirable to develop a small-molecule IL-4 antagonist.

SUMMARY OF THE INVENTION

In a first aspect, this invention provides compounds of formula I compound of formula I:



(I)

where:

A-B is selected from the group consisting of $-CHR^X-CHR^X-$, $-CR^Y=CR^Y-$, $-CHR^Y-O-$, $-O-CHR^Y-$, $-CHR^Y-NHR^1-$, $-NHR^1-CHR^Y-$, $-NR^1-C(=O)-$, $-C(=O)-NR^1$, $-S(=O)_{0-2}-CHR^X-$, $-CHR^X-S(=O)_{0-2}-$, $-SO_2-NR^1-$, $-NR^1-SO_2-$, $-C(=O)-CHR^X-$, $-CHR^X-C(=O)-$, and cycloalkylene;

X and Y are independently absent or are $-CHR^X-$, $-CHR^X-CH_2-$, or $-CH_2-CHR^X-$, provided that at least one of X and Y is present;

each R^X is independently selected from the group consisting of hydrogen, hydroxy, alkyl, haloalkyl, aminoalkyl, guanidinoalkyl, alkoxy, amino, alkylamino, dialkylamino, cycloamino, alkylcarbonylamino, guanidino, carboxy, alkoxycarbonyl, and tetrazolyl;

each R^Y is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, carboxy, and alkoxycarbonyl;

each R^Z is independently selected from the group consisting of alkyl and C_{0-2} alkyl ω-substituted with a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 or 2 atoms may be heteroatoms selected from O, S, N, and NR^1, optionally

substituted with one or more substituents selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitrile, nitro, amino, alkylamino, dialkylamino, cycloamino, carbonylamino, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$;

each R^1 is independently selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen, halo and hydroxy;

R^3 is selected from the group consisting of $-C(=O)OH$, $-S(=O)_2OH$, $-PO_4HR^Z$, $-C(=O)NHOH$, $-C(=O)CH(OH)R^Z$, $-C(=O)NHS(=O)_2R^Z$, $-C(=O)NHOR^Z$, $-C(=O)N(OH)R^Z$, $-C(=O)NHC(=O)CF_3$, $-NHC(=O)NHS(=O)_2R^Z$, $-S(=O)_2NHC(=O)R^Z$, $-NHS(=O)_2NHC(=O)R^Z$, 1-R^1-1,2,3,4-tetrazol-5-yl, 5-R^1-1,2,3-triazol-4-yl, 3-R^1-1,2,4-triazol-5-yl, 2-R^1-1,2,4-triazol-3(4H)-on-5-yl, 5-hydroxypyrazolyl, 5-hydroxyisothiazolyl, 5-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxazolidinyl, *N*-H-succinimidyl, *N*-H-hydantionyl, *N*-H-thiazolidindionyl, and 3-hydroxypyrrole-2,5-dionyl;

R^4 is selected from the group consisting of hydrogen, hydroxy, amino, alkylamino, dialkylamino, and cycloamino;

R^5 is selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, alkoxy, amino, alkylcarbonylamino, alkylsulfonylamino, benzenesulfonylamino, toluenesulfonylamino, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloaminocarbonyl, and alkoxycarbonyl, or is R^3;

R^6 is selected from the group consisting of hydrogen, halo and hydroxy,

or R^5 and R^6 together with the atoms to which they are attached form a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 to 4 atoms may be heteroatoms selected from O, $S(=O)_{0-2}$, $N(-O)_{0-1}$, and $NR^1(-O)_{0-1}$;

R^8, R^9, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, methoxy, and ethoxy;

R^{19} is hydrogen or is a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 or 2 atoms may be heteroatoms selected from O, S, N, and NR^1, optionally substituted with one or more substituents selected from the group consisting of

hydroxy, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, aminocarbonyl, alkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$; and the pharmaceutically acceptable salts of all these compounds.

In a second aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of at least one compound of this invention. These compositions find particular use as anti-asthmatic and anti-allergenic agents; and in the treatment of osteoporosis, osteoarthritis, rheumatoid arthritis, and autoimmune and other inflammation related disorders, and for therapeutically desirable immunosuppression.

In a third aspect, this invention provides a method of treating an animal having a disease capable of treatment by administration of an IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of at least one compound of this invention, optionally in conjunction with at least one other conventional therapeutic agent for the disease being treated.

In a fourth aspect, this invention provides methods of preparing the compounds of this invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

"Alkyl" means a linear monovalent hydrocarbyl group having 1 to 5 carbon atoms, or a branched or cyclic hydrocarbyl group having 3 to 5 carbon atoms. Exemplary alkyl groups include methyl, ethyl, isopropyl, cyclopropyl, *tert*-butyl, cyclopropylmethyl, and pentyl. "Alkoxy" means the group –O-alkyl, where "alkyl" is as defined immediately before.

"Carboxylate isosteres" means those moieties that are members of R^3 as listed above in the Summary of the Invention except carboxylate itself. Such carboxylate isosteres are well known to persons of ordinary skill in the art and are used when an acidic moiety is desired.

"Cycloalkylene" means a cyclic hydrocarbyl group having 5 to 7 ring carbon atoms, bonded to an aryl group or other linker atom at both of two adjacent ring carbon atoms; such as 1,2-cyclohexylene. "Cycloalkylene also includes those compounds where the bond between the ring carbon atoms that are bonded to the aryl groups or other linker atoms is a double bond. "Cycloalkylene" specifically includes cyclic compounds as defined immediately before where 1 or 2 of the ring carbon atoms are replaced by O, S, NH, or N-alkyl; such as 2,3-piperidinylene and 3,4-tetrahydropyranylene.

"Cycloamino" means a cyclic amino group having 5 to 7 ring atoms of which at least one is nitrogen and the remainder may all be carbon (e.g. pyrrolidino, piperidino) or one carbon may be replaced by O, S, NH, or N-alkyl (e.g. morpholino, piperazino, and the like).

"Animal" includes humans and non-human mammals, such as companion animals (cats, dogs, and the like) and farm animals (cattle, horses, sheep, goats, swine, and the like).

"Disease" includes any unhealthy condition of an animal, including particularly asthma, allergies, osteoporosis, osteoarthritis, rheumatoid arthritis, and autoimmune and other inflammation related disorders.

"Guanidino" means the group –NH-C(=NH)NH_2.

"Halogen" means fluorine, chlorine, or bromine; and "halo" likewise means fluoro, chloro, or bromo. "Haloalkyl" means alkyl (as that term is defined above) substituted with 1 to 5 halogen atoms, especially fluorine or chlorine atoms.

"Optionally fluorinated methoxy" and "optionally fluorinated ethoxy" mean a methoxy group substituted with 0-3 fluorine atoms and an ethoxy group substituted with 0-5 fluorine atoms respectively.

"Pharmaceutically acceptable excipient " means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients may be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous.

"Pharmaceutically acceptable salts" means salts that are pharmaceutically acceptable and have the desired pharmacological properties. Such salts include salts that may be formed where acidic protons present in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with the alkali metals, e.g. sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, e.g. ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (e.g. hydrochloric and hydrobromic acids) and organic acids (e.g. acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). When there are two acidic groups present, a pharmaceutically acceptable salt may be a mono-acid-mono-salt or a di-salt; and similarly where there are more than two acidic groups present, some or all of such groups can be salified.

A "protecting group" has the meaning conventionally associated with it in organic synthesis, i.e. a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete.

A "therapeutically effective amount" means the amount that, when administered to an animal for treating a disease, is sufficient to effect treatment for that disease.

"Treating" or "treatment" of a disease includes preventing the disease from occurring in an animal that may be predisposed to the disease but does not yet experience or exhibit symptoms of the disease (prophylactic treatment), inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease).

The compounds of this invention may possess one or more chiral centers or olefinic bonds, and, if they do, can therefore be produced as individual stereoisomers or as mixtures of stereoisomers, depending on whether individual stereoisomers or mixtures of stereoisomers of the starting materials are used. Unless indicated otherwise, the description or

naming of a compound or group of compounds is intended to include both the individual stereoisomers or mixtures (racemic or otherwise) of stereoisomers. Methods for the determination of stereochemistry and the separation of stereoisomers are well known to a person of ordinary skill in the art [*see* the discussion in Chapter 4 of J. March, "Advanced Organic Chemistry", 4th ed., John Wiley and Sons, New York, NY, 1992].

Implicit hydrogen atoms are omitted from the formulae for clarity, but should be understood to be present.

Presently Preferred Compounds

While the broadest definition of the invention is set out in the Summary of the Invention, certain compounds of this invention are presently preferred.

Presently preferred compounds of the invention are those where one or more of the following conditions are met:

(1) X and Y are independently absent or are $-CHR^X-$, provided that at least one of X and Y is present;

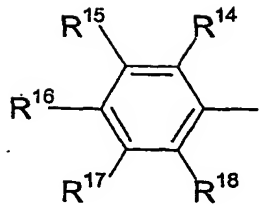
(2) R^3 is carboxy;

(3) R^4 is hydrogen or hydroxy, especially hydroxy; and

(4) R^2, R^8, and R^9 are hydrogen;

(5) R^{19} is an aromatic ring of 5 or 6 ring atoms of which 1 or 2 are heteroatoms selected from O, S, N, and NR^1, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, aminocarbonyl, alkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$, preferably where at least one substituent is present;

(6) R^{19} is phenyl optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, aminocarbonyl, alkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$, preferably where at least one substituent is present, especially R^{19} is



and R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} are independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, methoxy, and ethoxy, preferably where at least R^{16} is not hydrogen;

(7) R^{14} and R^{15} are hydrogen; and

(8) R^{16}, R^{17}, and R^{18} are independently hydrogen, fluorine, or trifluoromethyl, preferably where at least R^{16} is not hydrogen;

and the pharmaceutically acceptable salts thereof.

More preferred compounds are those where two or more of the above preferences are met.

Pharmacology and Utility

The compounds of this invention are antagonists of IL-4 signaling. Their activity as IL-4 signaling antagonists *in vitro* can be measured by methods such as the STAT6 phosphorylation assay discussed in J. Hon et al., *Science*, **265**, 1701-1706 (1994), F. W. Quelle et al., *Mol. Cell Biol.*, **15**, 3336-3343 (1995), and K. Takeda et al., *Nature*, **380**, 627-630 (1996); and as discussed in Example 3. Their activity can be measured *in vivo* by activity in the cynomolgus monkey primate model described in C.D. Wegner et al., "Models of Pulmonary Disease: Acute and Chronic Allergic Asthma in the Monkey and Acute and Chronic Viral Pulmonitis in the Mouse" in "Current Protocols in Pharmacology", John Wiley & Sons, 1998, 5.2.1-5.2.19.

The therapeutic ratio of a compound can be determined, for example, by comparing the dose that gives effective anti-asthmatic or anti-allergic activity in a suitable *in vivo* model such as the cynomolgus model described in Wegner et al., with the dose that gives significant weight loss (or other observable side-effects) in the test animal species.

Pharmaceutical compositions and administration

In general, compounds of this invention will be administered in therapeutically effective amounts by any of the usual modes known in the art, either singly or in combination with at least one other compound of this invention and/or at least one other conventional therapeutic agent for the disease being treated. A therapeutically effective amount may vary widely depending on the disease, its severity, the age and relative health of the animal being treated, the potency of the compound(s), and other factors. Therapeutically effective amounts of compounds of this invention may range from approximately 0.01-100 mg/Kg body weight. A person of ordinary skill in the art will be able without undue experimentation, having regard to that skill and this disclosure, to determine a therapeutically effective amount of a compound of this invention for a given disease.

In general, compounds of this invention will be administered as pharmaceutical compositions by one of the following routes: oral, topical, systemic (e.g. transdermal, intranasal, by inhalation, or by suppository), or parenteral (e.g. intramuscular, subcutaneous, or intravenous injection). Compositions may take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions; and comprise at least one compound of this invention in combination with at least one pharmaceutically acceptable excipient. Suitable excipients are well known to persons of ordinary skill in the art, and they, and the methods of formulating the compositions, may be found in such standard references as A.R. Alfonso, "Remington's Pharmaceutical Sciences", 17th ed., Mack Publishing Company, Easton PA, 1985. Suitable liquid carriers, especially for injectable solutions, include water, aqueous saline solution, aqueous dextrose solution, and glycols.

Typically, compounds of this invention will be administered orally, by inhalation (especially for asthma and in pulmonary inflammatory conditions), or topically (especially for psoriasis). The amount of a compound of this invention in the composition may vary widely depending on the type of composition, size of a unit dosage, kind of excipients, and other factors well known to those of ordinary skill in the art. In general, the final composition may comprise from 0.0001 percent by weight (%w) to 10 %w of the compound of this invention, preferably 0.001 %w to 1 %w, with the remainder being the excipient or excipients.

A composition may optionally contain, in addition to a compound of this invention, at least one other compound of this invention, and/or at least one other agent for the disease state being treated.

Preparation of the Compounds of this Invention

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or are prepared by methods well known to a person of ordinary skill in the art following procedures described in such references as Fieser and Fieser's "Reagents for Organic Synthesis", vols. 1-17, John Wiley and Sons, New York, NY, 1991; Rodd's "Chemistry of Carbon Compounds", vols. 1-5 and supplements, Elsevier Science Publishers, 1989; "Organic Reactions", vols. 1-40, John Wiley and Sons, New York, NY, 1991; March's "Advanced Organic Chemistry", 4th ed., John Wiley and Sons, New York, NY, 1992; and Larock's "Comprehensive Organic Transformations", VCH Publishers, 1989. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to a person of ordinary skill in the art having regard to that skill and this disclosure. In particular, the methods for protection and deprotection of intermediates and final products, and the synthesis of compounds containing carboxylate isosteres (either from an intermediate or product containing a carboxylate group or through the use of a starting material containing a carboxylate isostere rather than a carboxylate group) are well known to a person of ordinary skill in the art having regard to that skill and appropriate reference documents.

The starting materials, intermediates, and compounds of this invention may be isolated and purified using conventional techniques, including filtration, distillation, crystallization, chromatography, and the like. They may be characterized using conventional methods, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range between about 0 °C and 125 °C.

General synthetic methods are discussed below.

Typically, an appropriately substituted biphenyl or biphenyl ether is reacted with an appropriately substituted benzene to form the linker -X-A-B-Y- between the biphenyl/biphenyl ether and the benzene.

Where -A-B- is $-CR^Y=CR^Y-$, the alkene-containing linker is readily prepared by the either of two methods. In the first method, a suitably substituted aryl aldehyde or ketone is reacted with the sodium salt of a suitably substituted triphenylphosphonium halide (Wittig reaction), prepared from the corresponding haloaryl compound. Thus, for example, a suitably substituted benzyltriphosphonium halide (prepared from the corresponding benzyl bromide) dissolved in a solvent such as tetrahydrofuran is treated with a solution of *n*-butyllithium at 0 °C, stirred at room temperature, then the suitably substituted biphenylaldehyde is added. The aryl aldehyde or ketone may be commercially available or may be prepared by methods such as reduction of the corresponding carboxylic acid or oxidation of the corresponding alcohol. The haloaryl analog may be available commercially, or may be synthesized by from the corresponding alcohol. The reaction is quenched with methanol, extracted, dried, and the extracts concentrated to yield the olefin-linked compound. In the second method, a suitably substituted aryl halide or triflate and a suitably substituted vinylarene (the Heck coupling reaction), arylboronic acid (the Suzuki coupling reaction), or aryl halide and aryl trialkyltin (the Stille coupling reaction) are reacted in the presence of a Pd catalyst. Substituted analogs may be prepared analogously.

Where -A-B- is $-CHR^X-CHR^X-$, the alkyl linker is readily prepared by reduction of the corresponding alkene linker (see above) by any number of common reagents including H_2(g) over Pd/C. Substituted analogs of the alkyl linker may be prepared by a variety of means known to a person of ordinary skill in the art. For example, the ketone linkage (see below) may be alkylated at the site neighboring the ketone functional group by combination with an electrophile in the presence of base. The ketone functional group may be converted to an amino group by reductive amination. The ketone linkage may also be converted to a substituted alkene linkage by reaction with the sodium salt of an appropriately substituted triphenylphosphonium halide reagent or similar. The hydroxyl group of the linkage sited as

the precursor to the ketone may alternatively be converted to an ether or ester moiety by methods familiar to a person of ordinary skill in the art.

Where -A-B- is $-CHR^Y-O-$ or $-O-CHR^Y-$, the ether linker may be prepared by any of three methods. In the first method, a suitably substituted aryl alcohol may be combined in the presence of base with an appropriately substituted halomethyl arene or the activated (e.g. mesylate or tosylate) ester of an appropriately substituted hydroxymethyl arene. In the second method, an appropriately substituted aryl alcohol may be combined with an appropriately substituted hydroxymethyl arene in the presence of triphenylphosphine and diethyl azodicarboxylate (the Mitsunobu reaction). In the third method, an appropriately substituted aryl halide may be combined with an appropriately substituted hydroxymethyl arene in the presence of sodium *tert*-butoxide and a Pd-based catalyst (Buchwald coupling conditions). Similar preparations afford linkers where R^Y is other than hydrogen.

Where -A-B- is $-NR^1-C(=O)-$ or $-C(=O)-NR^1-$, the amide linker may be prepared by either of two methods. In the first method, a suitably substituted arylamine is combined with a suitably substituted arylcarboxylic acid in the presence of one of a variety of condensation reagents known to a person of ordinary skill in the art, such as EDCI, HOBT, HATU, CDI, and the like. In the second method, a suitably substituted arylamine is combined with a suitably substituted activated arylcarboxylic acid derivative, such as an arylcarboxylic acid halide, under Weinreb conditions.

Where -A-B- is $-S(=O)_{0-2}-CHR^X-$ or $-CHR^X-S(=O)_{0-2}-$, the thioether linkage may prepared by the combination of a suitably substituted arenethiol with a suitably substituted halomethyl arene or activated ester of a suitably substituted hydroxymethyl arene. The sulfoxide linkage is prepared by single oxidation of the thioether linkage by any of a variety of mild oxidation reagents known to a person of ordinary skill in the art, such as metachloroperbenzoic acid. The sulfone linkage is prepared from either the thioether or the sulfoxide by treatment with any of a variety of stronger oxidation reagents also known to a person of ordinary skill in the art, such as sodium periodate.

Where -A-B- is $-SO_2-NR^1-$ or $-NR^1-SO_2-$, the sulfonamide linkage may be prepared by reaction of a suitably substituted arylamine with a suitably substituted arenesulfonyl

halide, which may in turn be first prepared from the appropriately substituted arenesulfonic acid by one of a variety of methods known to a person of ordinary skill in the art; or by alkylation of a suitably substituted aryl sulfonamide with an aryl halide in the presence of a base.

Where -A-B- is -C(O=)-CHR^X- or -CHR^X-C(=O)-, the ketone linkage is prepared by oxidation of the corresponding hydroxyl substituted linkage by the use of MnO_2 or any other of a variety of oxidizing reagents known to a person of ordinary skill in the art. The hydroxy substituted linkage can be prepared by reaction of a suitably substituted aryl aldehyde with a suitably substituted arylmagnesium halide, prepared in advance from the corresponding aryl halide (the Grignard reaction).

Where -A-B- is 1,2-cycloalkylene, the cycloalkylene linkage containing a double bond between the bonding ring carbons may be prepared by the reaction of a 1,2-dihalocycloalkene sequentially with the appropriately substituted arylboronic acids (Suzuki coupling reaction) or aryl trialkyltin reagents (Stille coupling reaction) in the presence of a Pd catalyst. The reduced cycloalkylene linkage may be prepared by reduction of the corresponding double-bonded linkage by reaction with H_2 (g) over Pd/C. In large part the cycloalkylene linkages where there are hetero atom(s) in the ring may be prepared in the same manner. Additional methods commonly used by persons of ordinary skill in the art to prepare a variety of 1,2-diaryl substituted cyclic moieties, too numerous to describe in detail here, can be found in "Heterocyclic Chemistry, 2nd, ed." T. L. Gilchrist, 1992, Longman Scientific and Technical, Essex; and "Heterocyclic Chemistry, 3d ed." J. A. Joule, K. Mills, and G. F. Smith, 1995, Chapman and Hall, London.

A representative few further techniques are as follows:

When -X-A-B-Y- is -CHR^X-CH(OH)-CHR^Y-, the 2-hydroxypropyl linkage may be prepared by the reaction of a suitably substituted arylacetaldehyde with a suitably substituted arylmethylmagnesium halide, prepared from the corresponding arenylmethyl halide (the Grignard coupling reaction).

When -X-A-B-Y- is -CHR^X-NR^1-C(=O)-, the amidomethyl linkage may be prepared by the reaction of a suitably substituted arenecarboxylic acid or activated arenecarboxylic acid derivative with an appropriately substituted aminomethylarene, under conditions described above for the A-B linked amide case. When -X-A-B-Y- is -CHR^X-C(=O)-NR^1-, the amidomethyl linkage may be prepared by the reaction of a suitably substituted areneacetic acid or activated areneacetic acid derivative with an appropriately substituted aminoarene, under the same conditions. When -X-A-B-Y- is CH_2-CHR^X-NR^1-C(=O)-, the amidoethyl linkage may be prepared by the reaction of a suitably substituted arenecarboxylic acid or activated arenecarboxylic acid derivative with an appropriately substituted aminoethylarene, and when -X-A-B-Y- is -CH_2-CHR^X-C(=O)-NR^1-, the amidoethyl linkage may be prepared by the reaction of a suitably substituted areneпropionic acid or activated areneпropionic acid derivative with an appropriately substituted aminoarene, under the same conditions.

When -X-A-B-Y- is –CHR^Y-O-CHR^Y-, the C-O-C ether linkage may prepared by combination of the appropriately substituted hydroxymethyl arene with the appropriately substituted halomethyl-, methanesulfonyloxy-, or *p*-toluenesulfonyloxymethyl arene in the presence of base; and similarly when -X-A-B-Y- is -CH_2-CHR^Y-O-CHR^Y-.

It will be evident that the biphenyl linkage may be formed either before or after the formation of the -X-A-B-Y- linkage.

When R^{19} is an aromatic ring, the biaromatic moiety may be available commercially, or alternatively may be assembled either prior to or subsequent to the assembly of the -X-A-B-Y- linkage by reactions such as a coupling reaction between the appropriately substituted aryl halide or triflate and an arylboronic acid (Suzuki coupling reaction) or an aryltriphenyltin reagent (Stille coupling reaction) in the presence of a palladium catalyst.

It will also be evident that the phenyl rings may be substituted with substituents inert to the reaction conditions (or substituents protected against the reaction conditions associated with formation of the compound skeleton, where the protecting group can be removed without adverse effect on the remainder of the compound) without affecting the reactions described.

When a substituent is, for example, a carboxylic acid, it will typically be protected throughout the synthesis as an alkyl, e.g. C_{1-4} alkyl ester, typically the methyl ester; with the ester being removed in the final deprotection step by reaction with an aqueous base, such as aqueous lithium hydroxide. When a substituent is or contains an amine or guanidino group, it will typically be protected with a typical amine-protecting group well known to a person of ordinary skill in the art, such as *tert*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ), 9-fluorenylmethoxycarbonyl (FMOC), and the like, if needed, with the protecting group being removed in the final deprotection step by such methods as are conventional for removal of these amine-protecting groups. Under some circumstances, a carboxylic acid may be protected as an ester that is differentially removable, i.e. removable under circumstances where other carboxyl groups remain protected. When a substituent is a hydroxy group, it will typically be protected with a typical hydroxy-protecting group such as a tertiary silyl group, e.g. *tert*-butyldimethylsilyl. The choice of suitable protecting groups for substituents during the syntheses will be within the skill of a person of ordinary skill in the art having regard to that skill and this disclosure.

When a substituent is a carboxylate isostere, it may be prepared either from an intermediate or product containing a carboxylate group (by conversion of the carboxylate group to the isostere) or through the use of a starting material containing a carboxylate isostere rather than a carboxylate group; and such materials and reactions are well known to a person of ordinary skill in the art having regard to that skill and appropriate reference documents.

It will be apparent to a person of ordinary skill in the art, having regard to that skill, this disclosure, and the references cited herein, that generally any one of several different methods may be employed for the synthesis of a selected compound of this invention. For convenience, the synthesis may well be chosen based on the availability or cost of the starting materials and reagents for the methods available for that compound, or considering the number of steps necessary for the method. For example, if an appropriately substituted biphenyl or biphenyl ether is readily available or synthesizable, it may well be convenient to form the biphenyl /biphenyl ether linkage before formation of the -X-A-B-Y- linkage; but otherwise it may be preferable to form the biphenyl linkage later. A

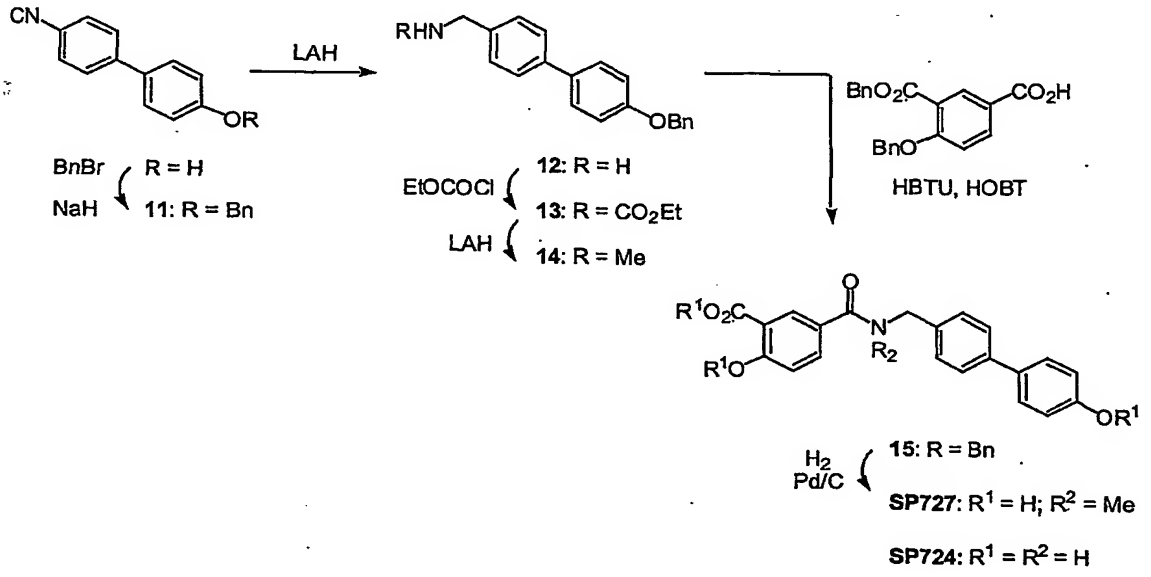
person of ordinary skill in the art, having regard to that skill, this disclosure, and the references cited herein, will be able to prepare desired compounds of formula I without undue experimentation.

Examples

The following non-limiting examples illustrate the invention. All commercially available materials were used as received. All synthesized compounds were characterized by ^{1}H NMR (Bruker DMX 400 MHz Spectrometer) and high-performance liquid-chromatography/mass-spectroscopy (HPLC-MS, Hewlett-Packard Series 1100 MSD), and judged to be at least 95% pure before testing in enzymatic assays.

Example 1

6-Hydroxy-*N*-(4′-hydroxybiphenyl-4-ylmethyl)-*N*-methylisophthalamic acid, SP727, and 6-Hydroxy-*N*-(4′-hydroxybiphenyl-4-ylmethyl)isophthalamic acid, SP724



To 4′-hydroxy-4-biphenylcarbonitrile (3.0 g, 15.4 mmol) in DMF (45 mL) was added portionwise NaH (676 mg, 16.9 mmol, 60% disp. in mineral oil). The mixture was stirred for 5 minutes. When no further H_2 evolution was observed, benzyl bromide (2.01 mL, 16.9 mmol) was added and the reaction was stirred at room temperature overnight. Solvent was

removed and the resulting oil was partitioned between EtOAc and H_2O. The aqueous layers were extracted with EtOAc (3x) and the combined organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to afford 4.0 g (91%) of benzyl ether **11** as an off-white solid.

To nitrile **11** (3.0 g, 10.5 mmol) in THF (35 mL) at 0 °C was added dropwise $LiAlH_4$ (15.8 mL, 15.8 mmol, 1.0 M in THF). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by dropwise addition of H_2O (836 μL), followed by NaOH (836 μL, 15% in H_2O) and by a final addition of H_2O (2.5 mL). The resulting slurry was filtered and washed with THF (3x). The filtrate was concentrated *in vacuo* to yield 2.6 g (85%) of amine **12** as a white solid.

To amine **12** (500 mg, 1.7 mmol) and DIEA (602 μL, 3.5 mmol) in dioxane (6 mL) at 0 °C was added slowly ethyl chloroformate (330 μL, 3.5 mmol). The reaction mixture was warmed to room temperature and stirred 2 h. The reaction was diluted with EtOAc and partitioned with 1M HCl. The aqueous layer was extracted with EtOAc (3x), and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 432 mg of carbamate **13** as a pale yellow solid (70% yield).

To **13** (417 mg, 1.2 mmol) in THF (4 mL) at 0 °C was added dropwise $LiAlH_4$ (1.7 mL, 1.7 mmol, 1.0 M in THF). The reaction was refluxed overnight and then worked up using the method described above. The slurry was filtered and washed with THF (3x). The filtrate was concentrated *in vacuo* to yield 340 mg (97%) of methylamine **14** as a white solid.

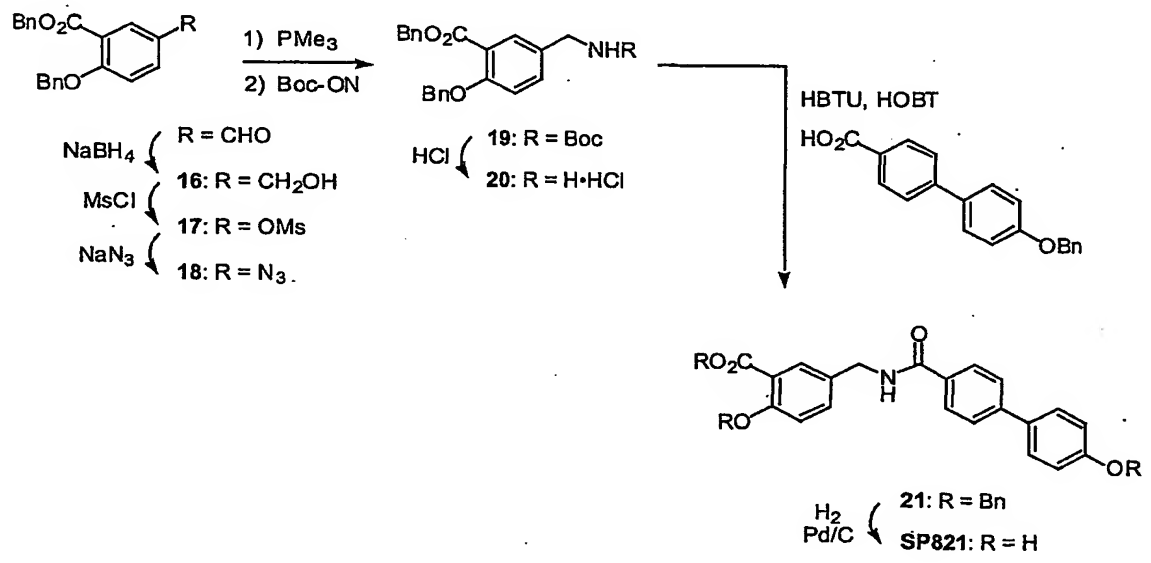
To 4-benzyloxy-3-benzyloxycarbonylbenzoic acid (338 mg, 0.9 mmol) in DMF (4 mL) was added HBTU (425 mg, 1.1 mmol), HOBt monohydrate (172 mg, 1.1 mmol) and DIEA (391 μL, 2.2 mmol). To the activated acid solution was added methylamine derivative **14** (340 mg, 1.1 mmol) and the mixture was stirred at room temperature for 5 h. Solvent was removed and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were washed with 1M HCl, followed by saturated $NaHCO_3$. The organic extracts were dried over Na_2SO_4 and then concentrated *in vacuo* to afford 623 mg crude amide **15** as a brown oil (>100%).

To amide **15** (82 mg, 0.13 mmol) in a 1:1 mixture of MeOH:EtOAc (4 mL) was added Pd (65 mg, 10% on activated carbon). The reaction vessel was charged with $H_{2(g)}$ and the mixture was stirred at room temperature / atmospheric pressure for 2 hr. The reaction mixture was filtered over a pad of Celite and washed with MeOH (3x). The filtrate was concentrated *in vacuo* to afford 57 mg (>100%) of **SP727**. The crude product was purified via reverse phase preparative HPLC, and the structural identity and purity were confirmed by ^{1}H NMR and LCMS.

SP724 was prepared in the same manner as was **SP727** omitting the amine methylation steps. ^{1}H NMR (400 MHz, DMSO-d_6):δ 4.44 (d, 2H, J=5.1 Hz), 6.81 (d, 2H, J=8.5 HZ), 6.81 (d, 1H, J=8.7 Hz), 7.31 (d, 2H, J=8.0 Hz), 7.42-7.51 (m, 4H), 8.00 (d, 1H, J=7.3 Hz), 8.39 (s, 1H), 9.04 (s, 1H), 9.51 (s, 1H); LRMS: 364 $(M+1)^+$.

Example 2

2-Hydroxy-5-{[(4′-hydroxybiphenyl-4-carbonyl)amino]methyl)-benzoic acid, SP821



To 4-benzyloxy-3-benzyloxycarbonylbenzoic acid (4 g, 11.5 mmol) in EtOH (45 mL, 95%) was added portionwise $NaBH_4$ (481 mg, 12.7 mmol). The reaction was stirred at room temperature for 1 hr, at which point it was quenched with H_2O and partitioned with EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were

washed with H_2O. The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 3.6 g of benzyl alcohol **16** as a white solid (90% yield).

To alcohol **16** (2 g, 5.7 mmol) in CH_2Cl_2 (25 ml) at 0 °C was added Et_3N (1.0 mL, 7.5 mmol) followed by dropwise addition of mesyl chloride (533 μL, 6.9 mmol). The reaction mixture was warmed to room temperature and stirred 1.5 h. The mixture was diluted with CH_2Cl_2 and partitioned with 1M HCl. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic layer was dried over Na_2SO_4. The organic extracts were concentrated *in vacuo* to give 2.5 g (>100%) of mesylate **17** as a colorless oil.

To mesylate **17** (2.6 g, 6.0 mmol) in DMF (25 mL) was added sodium azide (781 mg, 12.0 mmol). The reaction was stirred at 60 °C overnight. The reaction mixture was cooled to room temperature and the solvent was removed. The residue was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford 2.1 g (94%) of azide **18** as a pale yellow solid.

To azide **18** (500 mg, 1.3 mmol) in anhydrous THF (4 mL) under N_2 was added via syringe trimethylphosphine (2.0 mL, 2.0 mmol, 1.0 M in THF). The reaction was stirred at room temperature 1.5 h. The reaction mixture was cooled to –20 °C , then BOC-ON (363 mg, 1.5 mmol) was slowly added as a solution in THF (1.5 mL). The reaction was warmed to room temperature and stirred overnight. The mixture was partitioned between Et_2O and H_2O, and the aqueous layer was extracted with Et_2O (3x). The combined organic layer was washed with 2M NaOH (2x), dried over Na_2SO_4 and concentrated *in vacuo* to afford 573 mg (99%) BOC-protected benzylamine derivative **19** as a tan oil. Purification by flash chromatography, eluting with 3:1 hexanes:EtOAc, provided 286 mg clear oil.

To BOC-protected amine **19** (286 mg, 0.66 mmol) was added HCl (3 mL, 4.0 M in dioxane). The reaction was stirred at room temperature 1 hr. Solvent was removed in vacuo to afford 275 mg benzylamine **20** as the HCl salt (>100% yield).

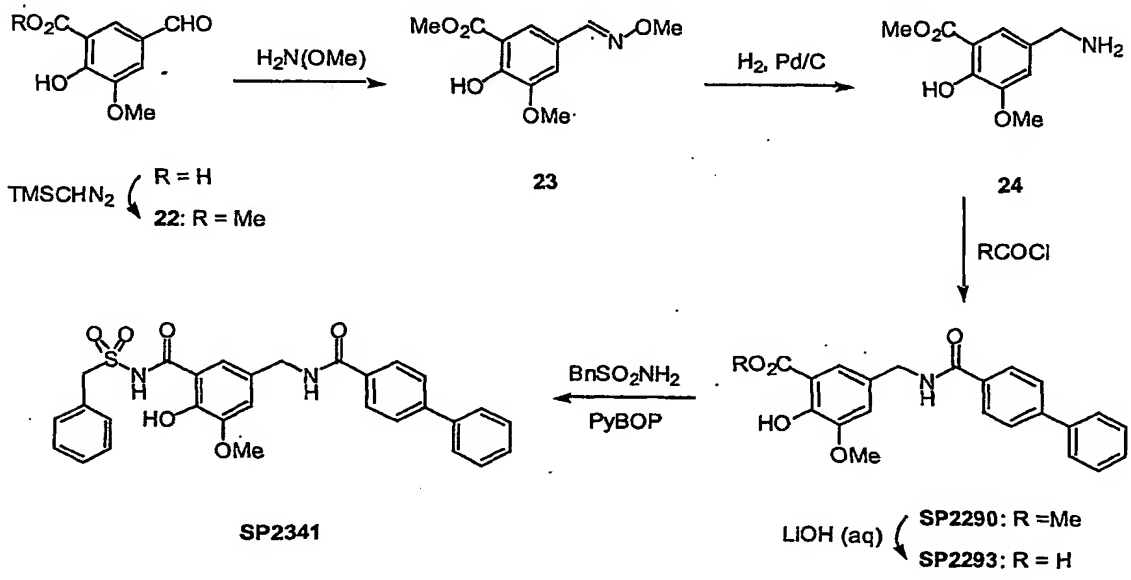
To 4-(4′-benxyloxy)benzoic acid (182 mg, 0.6 mmol) in DMF (2.5 mL) was added HBTU (271 mg, 0.72 mmol), HOBt monohydrate (110 mg, 0.72 mmol), and DIEA (333 μL,

1.9 mmol). To the activated acid solution was added benzylamine **20** (275 mg, 0.72 mmol) and the reaction was stirred overnight at room temperature. Solvent was removed and EtOAc was added to dissolve the residue, at which point an insoluble white solid precipitated. The solid was filtered, washed with EtOAc (1x) followed by THF (1x), and dried *in vacuo* to yield 185 mg of biphenyl amide **21** as a white solid (49% yield).

To amide **21** (80 mg, 0.13 mmol) in a 1:1 solution of MeOH:EtOAc (4 mL) was added Pd (60 mg, 10% on activated carbon). The flask was charged with H_2 and the reaction was stirred for 4 hr. The reaction mixture was filtered through Celite with methanol rinses. The filtrate was concentrated *in vacuo* to afford 55 mg (>100%) of debenzylated product **SP821** as a gray oil. The crude oil was purified via reverse phase preparative HPLC, and the structural identity and purity were confirmed by ^1H NMR and LCMS.

Example 3

Methyl 5-{[(Biphenyl-4-carbonyl)amino]methyl}-2-hydroxy-3-methoxybenzoate, SP2290, 5-{[(Biphenyl-4-carbonyl)amino]methyl}-2-hydroxy-3-methoxybenzoic acid, SP2291, and Biphenyl-4-carboxylic acid 4-hydroxy-3-methoxy-5-phenyl-methane-sulfonylamino-carbonylbenzylamide, SP2341



Trimethylsilyldiazomethane (10.0 mL of a 2 M solution in hexane, 20 mmol) was added dropwise to a rapidly stirred, heterogeneous mixture of 5-carboxyvanillin (1.78 g, 9.09 mmol) in a 1:1 mixture of dichloromethane and methanol. Additional $TMSCHN_2$ was added until no carboxyvanillin remained. Next, methoxyamine hydrochloride (4.64 g, 54.6 mmol) was added. After 18 h, the reaction mixture was concentrated until a thick precipitate formed. This material was removed by filtration, and the filtrate was concentrated to afford 2.10 g of 2-carboxymethyl-3-hydroxyl-*N*,4-dimethoxybenzaldoxime, **23** (100% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (app s, 9 H), 7.42 (s, 1 H), 7.48 (s, 1H), 7.97 (s, 1 H), 11.24 (s, 1 H). LRMS: 240 $(M+1)^+$.

A heterogeneous mixture of **23** (2.10 g, 10.0 mmol) and Pd/C (1.06 g of 10% Pd, 50% water, 0.500 mmol Pd) in 1:1 methanol/ ethyl acetate (100 mL) was placed under 1 atm. of H_2. Additional portions of catalyst were added over time until the reduction was complete, at which time the mixture was filtered through Celite. The filtrate was concentrated until a thick precipitate formed, and this material was isolated to afford 0.842 g of methyl 5-aminomethyl-2-hydroxy-3-methoxybenzoic acid, **24** (40% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 2 H), 3.80 (s, 3 H), 3.89 (s, 3 H), 7.22 (s, 1 H), 7.31 (s, 1 H). LRMS: 212 $(M+1)^+$.

A solution of 4-biphenylcarbonyl chloride (0.280, 1.29 mmol) in acetonitrile (25 mL) was added slowly to a solution of **24** (0.273 g, 1.29 mmol) and N-methylmorpholine (0.262 g, 2.58 mmol) in acetonitrile (25 mL) at 65 °C. After 1 h, the reaction was cooled to rt, and the residue was dissolved in EtOAc and passed through a short column of silica gel. The filtrate was concentrated to afford 0.447 g of **SP2290** as a white precipitate (88% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, 3 H), 3.88 (s, 3 H), 4.43 (d, J = 4.5 Hz, 2 H), 7.24 (s, 1 H), 7.33 (s, 1 H), 7.41 (t, J = 7.2 Hz, 1 H), 7.50 (app t, J = 7.2 Hz, 2 H), 7.74 (d, J = 7.5 Hz, 2 H), 7.79 (d, J = 7.6 Hz, 2 H), 7.98 (d, J = 7.6 Hz, 2 H), 9.09 (s, 1 H), 10.44 (s, 1 H). LRMS: 392 $(M+1)^+$.

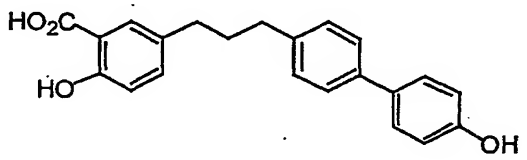
A cloudy slurry of **SP2290** (0.432 g, 1.10 mmol) in a saturated solution of lithium hydroxide monohydrate in methanol (70 mL) was diluted with 1:1 THF/ H_2O (30 mL) and stirred for 48 h. The reaction mixture was concentrated to remove the organic solvents,

cooled to 0 °C, and carefully acidified by the addition of 4 M HCl. The mixture was extracted with ethyl acetate (50 mL then 4 x 25 mL), and the combined extracts were dried over Na_2SO_4 and then concentrated to afford 0.374 g of **SP2293** (91% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3 H), 4.42 (d, J = 4.4 Hz, 2 H), 7.21 (s, 1 H), 7.33 (s, 1 H), 7.36-7.46 (m, 1 H), 7.50-7.55 (m, 2 H), 7.73 (d, J = 7.6 Hz, 2 H), 7.78 (d, J = 7.6 Hz, 2 H), 7.98 (d, J = 7.9 Hz, 2 H), 9.05-9.12 (bs, 1 H), 11.27-11.36 (bs, 1 H). LRMS: 78 $(M+1)^+$.

A clear, colorless solution of **SP2293** (0.127 g, 0.336 mmol) in DMF was treated sequentially with diisopropylethylamine (0.220 g, 1.68 mmol), benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (0.526 g, 1.01 mmol), and α-toluenesulfonamide (0.176 g, 1.01 mmol). After 22 h the reaction mixture was diluted with ethyl acetate (20 mL) and rinsed with 4 M HCl (4 mL). The aqueous layer was back-extracted with ethyl acetate (2 x 10 mL), and the combined extracts were rinsed with brine (3 mL) and dried over $MgSO_4$. Two sequential flash column chromatographic purifications eluting with 60:39:1 hexane/ ethyl acetate/ acetic acid, followed by precipitation from neat chloroform afforded 3.9 mg **SP2341** (2% yield). ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ□3.88 (s, 3H), 4.52 (s, 2 H), 4.58 (s, 2 H), 7.07 (s, 1 H), 7.28-7.33 (comp, 3 H), 7.37-7.44 (comp, 3 H), 7.53 (app s, 1 H), 7.63 (d, J = 7.8 Hz, 2 H), 7.68 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H). LRMS: 531 $(M+1)^+$.

Example 4

2-Hydroxy-5-[3-(4′-hydroxybiphenyl-4-yl)propyl]benzoic acid, SP549



SP549

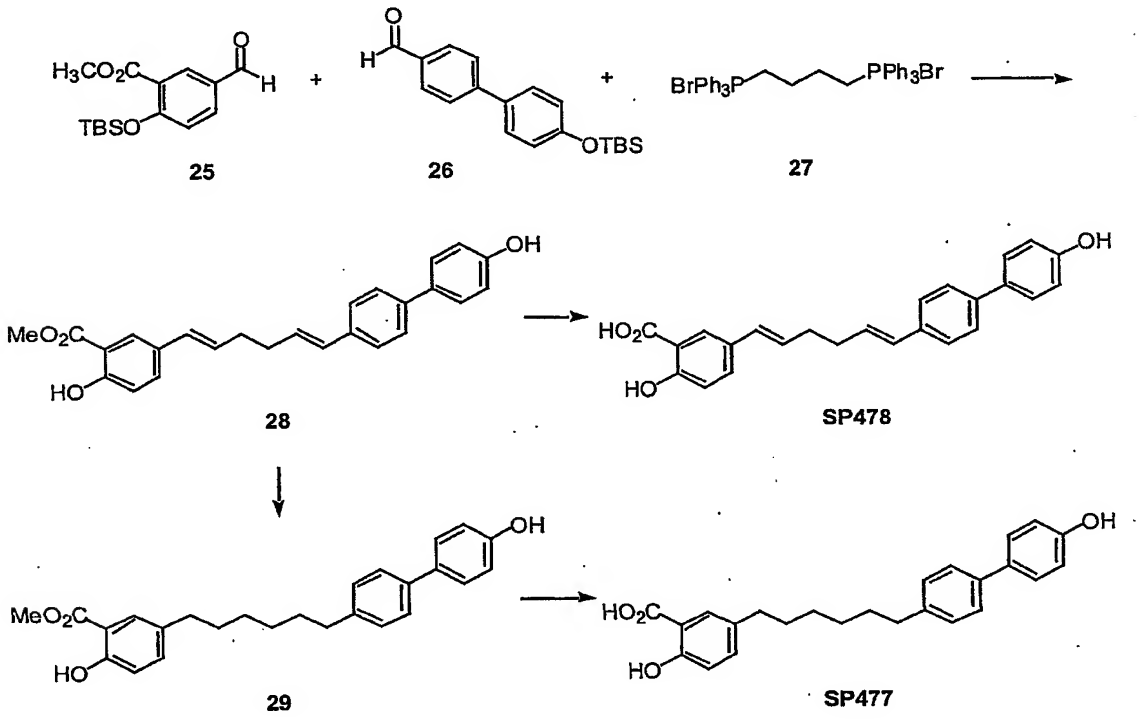
The title compound was prepared by alkylation of the appropriately protected 5-acetylsalicylic acid with the appropriately protected 4-(4′-hydroxyphenyl)benzylbromide, followed by reduction of the ketone and subsequent deprotections. ^{1}HNMR (400 MHz,

CD_3OD): 7.60 (s, 1H), 7.43-7.35 (m, 4H), 7.18-7.10 (m, 3H), 6.89 (d, 2H), 6.71 (d, 1H), 2.71-2.63 (m, 4H), 1.78 (m, 2H) MS: 348.

Example 5

2-Hydroxy-5-[6-(4′-hydroxybiphenyl-4-yl)hexyl]benzoic acid, SP477, and

2-Hydroxy-5-[6-(4′-hydroxybiphenyl-4-yl)hexa-1,5-dienyl]benzoic acid, SP478



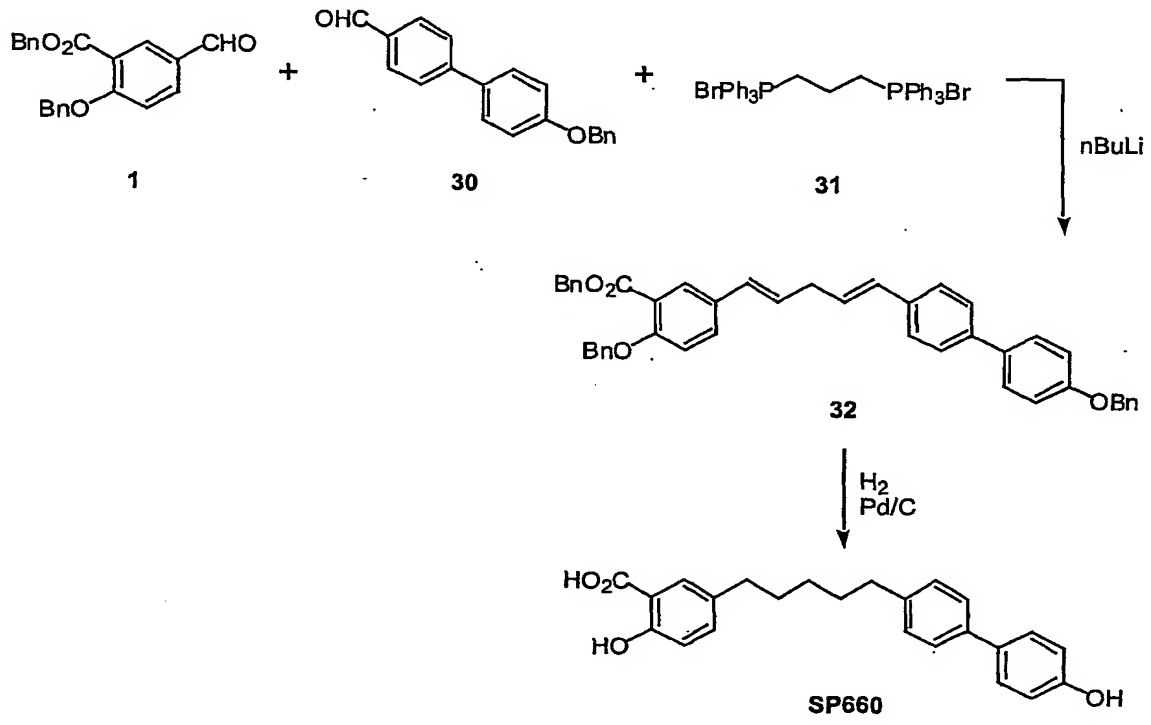
To a suspension of tetramethylenebis(triphenylphosphonium bromide) **27** (754 mg, 1 mmol) in THF (10mL) , 1 M *n*-BuLi (2 mL, 2 eq) was added at 0 °C . After stirring at RT for 60 min, A solution mixture of aldehyde **25** (294 mg, 1 mmol) and aldehyde **26** (312 mg, 1 mmol) in THF (3 mL) was added at 0 °C. The reaction was monitored by TLC until aldehyde was consumed. The reaction was quenched by the addition of MeOH, extracted with CH_2Cl_2/H_2O, dried over $NaSO_4$, and purified by flash column chromatography (10% EtOAc/hexanes) to afford 86 mg of **28** as a mixture of isomers. Hydrogenation of 28 by 10% Pd/C under H_2 at rt afforded methyl ester **29**. To a solution of **29** (14 mg, 0.035 mmol) in $MeOH/H_2O$, $LiOH{\cdot}H_2O$ (4.4 mg, 0.105 mmol) was added. The resulting solution was stirred

at 40 °C for 16 h. Purification by chromatography (10% MeOH/CH_2Cl_2) afforded 7.3 mg **SP477** as colorless solid (54% yield). ^{1}H NMR (CD_3OD) 7.68 (d, J=1.8 Hz, 1H), 7.42 (m, 4H), 7.17 (d, J=8.1 Hz, 1H), 7.13(dd, J=2.1, 8.3 Hz, 1H), 6.82 (d, J=8.6 Hz, 2H), 6.72 (d, J=8.3 Hz, 1H), 2.59 (t, J=7.5 Hz, 2H), 2.51 (t, J=7.5 Hz, 2H), 1.55-1.63 (m, 4H), 1.35 (bt, J=3.3 Hz, 4H). LCMS: 391.1 $(M+H)^+$.

To a solution of **28** (5.6 mg, 0.014 mmol) in MeOH/H_2O, $LiOH{\cdot}H_2O$ (5.8 mg, 0.14 mmol) was added. The resulting solution was stirred at 40 °C for 16 hr. Purification by chromatography (10% MeOH/CH_2Cl_2) to afforded 3.4 mg of **SP478** as colorless solid (64% yield). ^{1}H NMR (CD_3OD):δ 7.84 (d, J=1.9 Hz, 1H), 7.42-7.49 (m, 4H), 7.23-7.35 (m, 3H), 6.84 (d, J=8.5 Hz, 2H), 6.77 (d, J=8.4 Hz, 1H), 6.43 (d, J=11.4 Hz, 1H), 6.35 (d, J=11.6 Hz, 1H), 5.64-5.74 (m, 1H), 5.49-5.60 (m, 1H), 2.35-2.53 (m, 4H). LCMS: 387.15 $(M+H)^+$.

Example 6

2-Hydroxy-5-[5-(4′-hydroxybiphenyl-4-yl)pentyl]benzoic acid, SP660



To a suspension of trimethylenebis(triphenylphosphonium bromide) **31** (726 mg, 1 mmol) in THF (10mL), 1 M *n*-BuLi (2 mL, eq) was added at 0 °C. After stirring at rt for 60 min, a solution mixture of aldehyde **1** (336 mg, 1 mmol) and aldehyde **30** (288 mg, 1 mmol) in THF (3 mL) was added at 0 °C. The reaction was monitored by TLC until the aldehydes were consumed. The reaction was quenched by addition of MeOH, extracted by CH_2Cl_2/H_2O, dried ($NaSO_4$), and purified by flash column chromatography (5-10% EtOAc/hexanes) to afford 121 mg **32** as a mixture of cis/trans isomers(19 % yield). To a solution of **32** (64 mg 0.1 mmol) in MeOH (2 mL) 10% Pd-C (32 mg) was added. The resulting mixture was stirred under H_2 at rt for 2 hr, filtered through Celite, then purified by flash column chromatography (5-10 % MeOH/CH_2Cl_2) to afford 26 mg of **SP660** (69% yield). ^{1}H NMR (CD_3OD):δ 7.68 (d, J=1.8 Hz, 1H), 7.42 (d, J=8.2 Hz, 4H), 7.16(d, J=7.3 Hz, 2H), 7.11(dd, J=2.0, 8.3 Hz, 1H), 6.82 (d, J=8.5 Hz, 2H), 6.721 (d, J=8.3 Hz, 1H), 2.60 (t, J=7.2 Hz, 2H), 2.53 (t, J=7.2 Hz, 2H), 1.59-1.69 (m, 4H), 1.37 (tt, J=8.0, 8.0 Hz, 2H). LCMS: 377.1 $(M+H)^+$.

Other compounds, including compounds with carboxylate isosteres, were similarly prepared and may be similarly prepared.

Example 7

Inhibition of IL-4/IL-4R binding (STAT6 phosphorylation protocol)

Cell Culture. Ramos cells were grown in RPMI medium supplemented with 10% fetal bovine serum and antibiotics. Cells were split to 0.5 to 0.8 x10^6 cells/mL on the day before the assay. On the day of the assay, the cell concentration is approximately 1x10^6 cells/mL.

The concentration of IL-4 used in the assay was determined by carrying out a dose-response curve according to the protocol detailed below. IL-4 concentrations between 0.25 and 0.5 ng/mL result in STAT6 activation that is in the linear range of the assay.

Compound Testing. Compound testing was carried out in the absence of serum. The samples, made up as in the table (1 mL), were preincubated in 15 mL polypropylene conical tubes (Corning) at 37 °C for 30 minutes.

Sample	Compound	Growth Media
No treatment	None	1 mL RPMI no serum
IL-4 (0.25 ng/mL, final conc.) + vehicle	2 µL DMSO	1 mL RPMI no serum + 0.25 ng/mL IL-4
IL-4 (0.25 ng/mL, final conc.) + test compound	2µL of test compound in DMSO (stock conc.: 2, 0.4, 0.08, 0.016 m*M*)	1 mL RPMI no serum + 0.25 ng/mL IL-4

The Ramos cell concentration was determined; and the cells were centrifuged at 800 x g at room temperature for 5 minutes. The cells were resuspended in pre-warmed RPMI medium (without serum) to a concentration of 10 x 10^6 cells/mL. To each sample (1 mL) was added 1 mL of the cell suspension; and the samples were incubated at 37 °C for 30 minutes.

Protein Extracts. The samples were centrifuged at 800 x g at room temperature for 5 minutes. All medium was carefully removed from the cell pellet, which was placed on ice. The cells were then lysed with 50 µl of RIPA buffer containing protease and phosphatase inhibitors [150 m*M* NaCl, 50 m*M* Tris pH 8.0, 1.0% NP-40, 0.5% deoxycholate, 0.1% sodium dodecyl sulfate, 10 µg/mL aprotinin, 10 µg/mL antipain, 5 µg/mL leupeptin, 1 mg/mL Pefablock SC, 50 m*M* NaF, 80 m*M* sodium glycerophosphate, and 2 m*M* sodium vanadate (heat activated stock solution)).

The lysed cells were let sit on ice for 5-15 minutes, the pipetted several times and transferred to microcentrifuge tubes. The cells were fully lysed by carrying out 2 freeze (dry ice) thaw (room temperature) cycles or sonicating the extract on ice for 10 seconds with a probe sonicator, then centrifuged in a Brinkmann mucrocentrifuge at full speed at 4 °C for 15 minutes. The supernatant was removed and transferred to another tube; the protein extract was passed through a 26 gauge needle to completely shear all DNA in the extracts, and the protein concentration was quantitated using Bio-Rad protein assay dye reagent (Bio-Rad Laboratories, catalog #500-0006).

Immunoblotting. Protein extract (20 µg) was loaded onto a Novex (Novex, San Diego) mini-protein gel (NuPAGE gel, 4-12%) according to the manufacturer's instructions; and the gel subjected to electrophoresis at 180 V for 1 hour in MOPS buffer (supplied by Novex).

The gel was transferred to Novex PVDF membrane according to manufacturer's instructions. The PVDF membrane was blocked with 5% non-fat dry milk (NFDM) in TBST (8.00 g/L NaCl, 24.2 g/L Tris-base, 0.5% Tween 20, pH 7.6) for 1 hour.

Primary antibodies (Phospho STAT6, New England Biolabs) were diluted at 1:1000 in 5% BSA in TBST. The antibodies were incubated with the blot overnight at 4 °C; and the blot washed twice with TBST for 15-30 minutes each at room temperature.

The blot was then incubated with the appropriate secondary antibody (HRP conjugated goat anti-rabbit antibodies, Zymed, South San Francisco, CA) at 1:1000 in 0.5% NFDM in TBST for 2 hr at RT, and washed twice with TBST for 15-30 minutes each at room temperature. The blot was developed using ECL (Amersham International) plus Western blotting detection reagents in accordance with the manufacturer's instructions, and exposed to single emulsion Biomax film for 10 seconds to 10 minutes.

Compounds of this invention were active in this assay.

Example 8

Inhibition of IL-4/IL-4R binding (Indirect ELISA assay)

Receptor Coated Plates. Dispense 100 µL of 10 µg / mL NeutrAvidin (in 50 mM sodium carbonate, pH9) to Nunc Microsorp 96-well microtiter plates. Incubate overnight at 4°C to coat. Shake out solution and blot excess liquid from the inverted and tapped plate. Immediately add 200 µL SuperBlock (Pierce) per well. Shake hard briefly to block upper part of each well, then shake gently for 30 minutes. Again shake out solution and blot. Use a plate washer to rinse all the plates with a single 4 cycle rinse to remove residual avidin (use a program that leaves rinse solution in wells at end). Then, one plate at a time, shake and blot wash buffer, and immediately add 100 µL of 18 nM IL-4R biotin in SuperBlock supplemented with 0.01% Tween 20. Shake these plates gently for at least 1 hour to coat the receptor.

Compound Plates. Dispense 1.5 µL droplets of 200 mM solutions of the test compounds in DMSO to columns 1 through 11 in separate polypropylene plates. Separately, dispense 1.5 µL droplets of DMSO only to column 12 of each plate. Rapidly resuspend these droplets in

148.5 µL of 100 pM IL-4 in SuperBlock with 0.01% Tween 20, except for wells 12G and 12H. Manually add/mix 148.5 µL of SuperBlock with 0.01% Tween 20 and supplemented with 20 nM of IL-4R to the 12G wells to serve as positive control. Manually add/mix 148.5 µL of SuperBlock with 0.01% Tween 20 without IL-4 to the 12H wells to serve as background control.

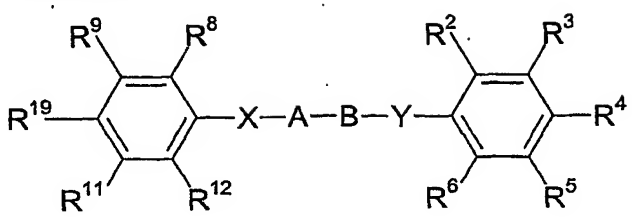
Assay. Rinse the receptor coated plates with a single 4 cycle rinse (use a program that leaves rinse solution in wells at end). After a 30 minute pre-incubation of the resuspended compound plates, shake and blot the rinsing solution from one of the receptor coated plates. Transfer 100 µL from each well of the compound plate to the same well of this receptor coated plate. Repeat for each plate so that the pre-incubation time of the compound solution is the same 30 minutes. After the plates have been further incubated for 1 hour, quickly rinse each one twice with 4-cycle rinses, and immediately add 100 µL of 2 nM anti-IL-4-mAb-HRP in SuperBlock with 0.01% Tween 20; working quickly one plate at a time to minimize the loss of bound IL-4. After these plates have been incubated another 1 hour, rinse each one twice with 4-cycle rinses and immediately add 100 µl of TMB/Peroxide substrate solution; working quickly one plate at a time to minimize the loss of bound mAb-HRP. Shake hard until the plate is fully developed, then add and mix in 100 µl 1M sulfuric acid. Read OD_{450} minus OD_{655} using a spectrophotometer. A positive result is shown by a yellow coloration.

Compounds of this invention were active in this assay.

While this invention has been described in conjunction with specific embodiments and examples, it will be apparent to a person of ordinary skill in the art, having regard to this disclosure, that equivalents of the specifically disclosed materials and techniques will also be applicable to this invention; and such equivalents are intended to be included within the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

where:

A-B is selected from the group consisting of $-CHR^X-CHR^X-$, $-CR^Y=CR^Y-$, $-CHR^Y-O-$, $-O-CHR^Y-$, $-CHR^Y-NHR^1-$, $-NHR^1-CHR^Y-$, $-NR^1-C(=O)-$, $-C(=O)-NR^1$, $-S(=O)_{0-2}-CHR^X-$, $-CHR^X-S(=O)_{0-2}-$, $-SO_2-NR^1-$, $-NR^1-SO_2-$, $-C(=O)-CHR^X-$, $-CHR^X-C(=O)-$, and cycloalkylene;

X and Y are independently absent or are $-CHR^X-$, $-CHR^X-CH_2-$, or $-CH_2-CHR^X-$, provided that at least one of X and Y is present;

each R^X is independently selected from the group consisting of hydrogen, hydroxy, alkyl, haloalkyl, aminoalkyl, guanidinoalkyl, alkoxy, amino, alkylamino, dialkylamino, cycloamino, alkylcarbonylamino, guanidino, carboxy, alkoxycarbonyl, and tetrazolyl;

each R^Y is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, carboxy, and alkoxycarbonyl;

each R^Z is independently selected from the group consisting of alkyl and C_{0-2} alkyl ω-substituted with a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 or 2 atoms may be heteroatoms selected from O, S, N, and NR^1, optionally substituted with one or more substituents selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitrile, nitro, amino, alkylamino, dialkylamino, cycloamino, carbonylamino, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$;

each R^1 is independently selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen, halo and hydroxy;

R^3 is selected from the group consisting of -C(=O)OH, -S(=O)$_2$OH, -PO$_4$HR^Z, -C(=O)NHOH, -C(=O)CH(OH)R^Z, -C(=O)NHS(=O)$_2R^Z$, -C(=O)NHOR^Z, -C(=O)N(OH)R^Z, -C(=O)NHC(=O)CF_3, -NHC(=O)NHS(=O)$_2R^Z$, -S(=O)$_2$NHC(=O)R^Z, -NHS(=O)$_2$NHC(=O)R^Z, 1-R^1-1,2,3,4-tetrazol-5-yl, 5-R^1-1,2,3-triazol-4-yl, 3-R^1-1,2,4-triazol-5-yl, 2-R^1-1,2,4-triazol-3(4H)-on-5-yl, 5-hydroxypyrazolyl, 5-hydroxyisothiazolyl, 5-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxazolidinyl, *N*-H-succinimidyl, *N*-H-hydantionyl, *N*-H-thiazolidindionyl, and 3-hydroxypyrrole-2,5-dionyl;

R^4 is selected from the group consisting of hydrogen, hydroxy, amino, alkylamino, dialkylamino, and cycloamino;

R^5 is selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, alkoxy, amino, alkylcarbonylamino, alkylsulfonylamino, benzenesulfonylamino, toluenesulfonylamino, carboxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloaminocarbonyl, and alkoxycarbonyl, or is R^3;

R^6 is selected from the group consisting of hydrogen, halo and hydroxy, or R^5 and R^6 together with the atoms to which they are attached form a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 to 4 atoms may be heteroatoms selected from O, S(=O)$_{0-2}$, N(-O)$_{0-1}$, and NR^1(-O)$_{0-1}$;

R^8, R^9, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, methoxy, and ethoxy;

R^{19} is hydrogen or is a saturated, unsaturated, or aromatic ring of 5 through 7 ring atoms, of which 1 or 2 atoms may be heteroatoms selected from O, S, N, and NR^1, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, aminocarbonyl, alkylaminocarbonyl, carboxy, alkoxycarbonyl, -S(=O)$_2$N$R^1{}_2$, and -NR^1S(=O)$_2R^1$;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 where

R^2, R^8, and R^9 are hydrogen; and

R^3 is carboxy;

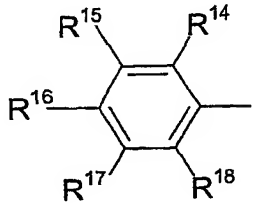
or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 where

R^{19} is phenyl or an aromatic ring of 5 or 6 ring atoms of which 1 or 2 are heteroatoms selected from O, S, N, and NR^1, each optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, aminocarbonyl, alkylaminocarbonyl, carboxy, alkoxycarbonyl, $-S(=O)_2NR^1{}_2$, and $-NR^1S(=O)_2R^1$;

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 where R^{19} is



and R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} are independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, methoxy, and ethoxy;

or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4 where

X and Y are independently absent or are $-CHR^X-$, provided that at least one of X and Y is present;

R^2, R^8, R^9, R^{14}, and R^{15} are hydrogen; and

R^3 is carboxy;

or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 5 where

R^4 is hydrogen or hydroxy; and

R^{16}, R^{17}, and R^{18} are independently hydrogen, fluorine, or trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a compound of Claim 1; and

(b) a pharmaceutically acceptable excipient.

8. A pharmaceutical composition comprising:
(a) a therapeutically effective amount of a compound of Claim 2; and
(b) a pharmaceutically acceptable excipient.

9. A pharmaceutical composition comprising:
(a) a therapeutically effective amount of a compound of Claim 3; and
(b) a pharmaceutically acceptable excipient.

10. A pharmaceutical composition comprising:
(a) a therapeutically effective amount of a compound of Claim 4; and
(b) a pharmaceutically acceptable excipient.

11. A pharmaceutical composition comprising:
(a) a therapeutically effective amount of a compound of Claim 5; and
(b) a pharmaceutically acceptable excipient.

12. A pharmaceutical composition comprising:
(a) a therapeutically effective amount of a compound of Claim 6; and
(b) a pharmaceutically acceptable excipient.

13. A method of treating an animal having a disease capable of treatment by administration of an IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 1.

14. A method of treating an animal having a disease capable of treatment by administration of an IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 2.

15. A method of treating an animal having a disease capable of treatment by administration of a IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 3.

16. A method of treating an animal having a disease capable of treatment by administration of a IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 4.

17. A method of treating an animal having a disease capable of treatment by administration of a IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 5.

18. A method of treating an animal having a disease capable of treatment by administration of a IL-4 antagonist, comprising administration to that animal of a therapeutically effective amount of a compound of Claim 6.

19. The method of Claim 13 where the disease state is selected from asthma, allergy, and autoimmune diseases.

20. The method of Claim 13 where the disease state is selected from osteoarthritis and rheumatoid arthritis.

21. Use of a compound of claim 1 in the manufacture of a medicament useful for treating a disease state in an individual capable of treatment by administration of an IL-4 antagonist.

22. Use of a compound of claim 21 wherein the disease state is selected from asthma, allergy, and autoimmune diseases.

23. Use of a compound of claim 21 wherein the disease state is selected from osteoarthritis and rheumatoid arthritis.